JACC Vol. 16, No. 1
July 1990:86–90

Ventricular Rate Control and Exercise Performance in Chronic Atrial Fibrillation: Effects of Diltiazem and Verapamil

TORBJÖRN LUNDSTRÖM, MD, LARS RYDÉN, MD, FACC

Skövde, Sweden

The effects of two calcium channel blockers, diltiazem (270 mg/day) and verapamil (240 mg/day), were studied in 18 patients with chronic atrial fibrillation. During 24 h Holter electrocardiographic monitoring, mean ventricular rate (beats/min) decreased from 88 ± 14 with placebo to 76 ± 13 ($p < 0.001$) with diltiazem and 80 ± 11 ($p < 0.01$) with verapamil. Maximal symptom-limited exercise tolerance (W) increased from 127 ± 39 during the placebo period to 136 ± 42 ($p < 0.01$) with diltiazem and 137 ± 39 ($p < 0.01$) with verapamil.

Ventricular rate and rate-pressure product were lower at rest and during exercise with diltiazem and verapamil than with placebo ($p < 0.001$), with the drugs being similarly effective. Ventricular rate at maximal exercise (beats/min) was 179 ± 13 with placebo compared with 159 ± 21 with diltiazem and 158 ± 23 with verapamil. Maximal oxygen uptake (ml/kg per min) was 22.3 ± 4.5 with placebo, 23.7 ± 4.9 ($p < 0.05$) with diltiazem and 22.9 ± 4.5 with verapamil (p = NS). Respiratory gas exchange anaerobic threshold was reached at a work load (W) of 76 ± 21 with placebo, 84 ± 27 ($p < 0.05$) with diltiazem and 85 ± 23 ($p < 0.01$) with verapamil.

In conclusion, patients with chronic atrial fibrillation have modestly improved exercise tolerance with calcium channel blockade therapy. The dromotropic responses and the effects on physical performance are of similar magnitude for diltiazem and verapamil.

(J Am Coll Cardiol 1990;16:86–90)

Chronic atrial fibrillation is characterized by a rapid increase in the ventricular rate during exercise (1). This may be detrimental to cardiac output because of impaired ventricular diastolic filling (2). Digoxin alone, acting primarily by causing an increase in vagal tone, often fails to control exercise-induced tachycardia in patients with atrial fibrillation (3). The calcium channel blockers diltiazem and verapamil increase refractoriness and prolong conduction time in the atrioventricular node. These agents may effectively decrease ventricular rate in atrial fibrillation both at rest and during exercise (4,5). Diltiazem is considered to have a less negative inotropic effect (6), a possible advantage in the treatment of atrial fibrillation.

One study (7) reported a substantial improvement in exercise capacity in patients with chronic atrial fibrillation after the administration of verapamil. In other investigations (8–10), neither diltiazem nor verapamil was reported to change exercise tolerance. A direct comparison of the two drugs, including gas exchange analysis, has to our knowledge, not been performed.

The aim of this study was to compare the effects of diltiazem and verapamil on ventricular rate response, maximal exercise tolerance and gas exchange variables during exercise in patients with chronic atrial fibrillation.

Methods

Study patients. Nineteen patients (13 men and 6 women, mean age 65 ± 5 years, range 55 to 74) with atrial fibrillation for ≥1 month (defined in this study as chronic atrial fibrillation) were included after providing informed consent. One patient did not complete the study protocol; thus, the results are obtained from 18 patients. Eleven of the 18 had lone atrial fibrillation, and 5 had one or more underlying cardiovascular disorders, including mitral stenosis (n = 1), surgically corrected mitral stenosis (n = 1), hypertension (n = 3), ischemic heart disease (n = 1) and left heart failure (n = 1). Two patients had mild chronic bronchitis. All patients were in New York Heart Association functional class I or II. Seventeen patients were treated with digoxin (0.13 [n = 3] and 0.25 mg [n = 14] daily). All antiarrhythmic drugs were discontinued before the start of the study.

From the Department of Cardiology, Central Hospital, Skövde, Sweden. This study was supported by grants from the Swedish Heart and Lung Foundation, Stockholm, Sweden and from the Department of Clinical Research, Ferrosan, Malmö, Sweden.

Manuscript received October 4, 1989; revised manuscript received December 13, 1989, accepted January 5, 1990.

Address for reprints: Torbjörn Lundström, MD, Department of Cardiology, Central Hospital, S-541 85 Skövde, Sweden.

0735-1097/90/$3.50

The study protocol was approved by the local Ethics Committee on Human Research and by the Swedish Social Board of Welfare.

Study design. After randomization, the patients entered a single-blind 3 week placebo period, followed by a double-blind crossover phase, comprising two treatment periods of 3 weeks each. During these periods, diltiazem (90 mg three times daily) or verapamil (80 mg three times daily) was administered, using a double-dummy technique. Possible side effects were assessed by active questioning at the end of each period. Blood samples for analysis of drug concentrations were also obtained. Serum digoxin was measured 24 h after the last dose by radioimmunoassay (11). The lowest standard used at our laboratory corresponds to 0.6 nmol/liter, and concentrations below that value are designated "<0.6." As a test of patient compliance, diltiazem and verapamil in plasma were estimated 2 to 4 h after the last dose, using high performance liquid chromatography (12) and gas chromatography–mass spectrophotometry (13), respectively. A 24 h Holter electrocardiogram (ECG) (Oxford Medilog System) was recorded. From this, the number of ventricular beats was calculated by an ECG analyzer (Reynolds Pathfinder). The mean ventricular rate (beats/min) was estimated for each 1 h interval and for the entire 24 h period.

A maximal symptom-limited exercise test was performed 3 to 5 h after the morning dose of drugs. Ventricular rate and blood pressure values at rest were obtained after 2 min of sitting. Patients exercised on a bicycle ergometer, starting with no load. Work load was subsequently increased by 1 W every 6 s, with the ECG continuously monitored during the test. Ventricular rate was determined by multiplying the number of QRS complexes per 30 s by 2. Blood pressure measurements were obtained using a sphygmomanometer and a Doppler device to record the pulse in the radial artery. The patient's subjective perception of exertion was evaluated by using the Borg 6 to 20 point scale (14).

Respiratory gas exchange variables were determined continuously throughout the exercise test using the Medical Graphics Corporation 2001 system. The analyses included oxygen uptake (ml/kg per min), minute ventilation (liters/min) and respiratory exchange ratio (carbon dioxide elimination/oxygen uptake). The data were processed by an average filter, and mean values over 15 s intervals were estimated. Points of analysis were at 50% and 80% of the maximal work load achieved during placebo treatment and at maximal exertion. The gas exchange anaerobic threshold determined as outlined by Beaver et al. (15) was taken as the mean of estimations performed by two independent observers who were unaware of other patient data.

Statistics. Data are presented as the mean value ± SD. Because the study had a crossover design, the main statistical tool was analysis of variance for repeated measurements. The analysis was completed with paired *t* tests or appropriate nonparametric tests. If not stated otherwise, the p values given refer to the comparison between either of the active treatments and the placebo period.

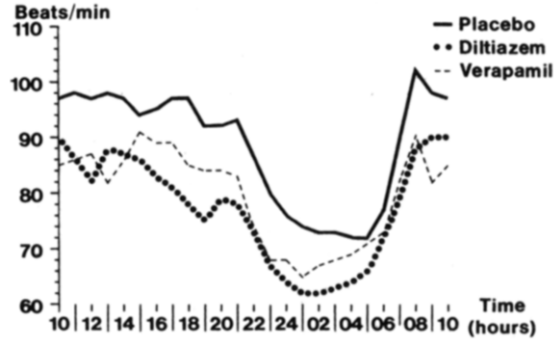


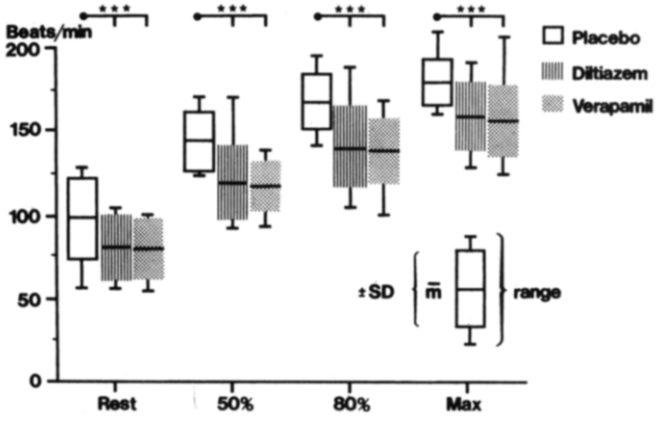
Figure 1. Mean hourly ventricular rates over 24 h in 18 patients.

Results

Ventricular rate, blood pressure and rate-pressure product. During ambulatory Holter recording (Fig. 1), the ventricular rate during 24 h was reduced from an average of 88 ± 14 beats/min during the placebo period to 76 ± 13 beats/min ($p < 0.001$) with diltiazem and 80 ± 11 beats/min ($p < 0.01$) with verapamil. Comparing ventricular rate at sitting rest and during exercise, active treatment resulted in a significant decrease ($p < 0.001$) of a similar magnitude for diltiazem and verapamil (Fig. 2). Ventricular rate at maximal exercise was 179 ± 13 with placebo, 159 ± 21 with diltiazem and 158 ± 23 beats/min with verapamil.

Systolic blood pressure (Fig. 3) was somewhat lower during active treatment, but similar for diltiazem and verapamil. The most pronounced decrease was seen at 80% work load (placebo 193 ± 22, diltiazem 184 ± 22 [$p < 0.05$] and verapamil 182 ± 24 mm Hg [$p < 0.01$]).

Figure 2. Ventricular rates during sitting (rest), at submaximal work loads corresponding to 50% and 80% of maximum during the placebo phase and at the maximal work load (Max) attained during each treatment. ***$p < 0.001$. $\bar{m}$ = mean.



JACC Vol. 16, No. 1
July 1990:86–90

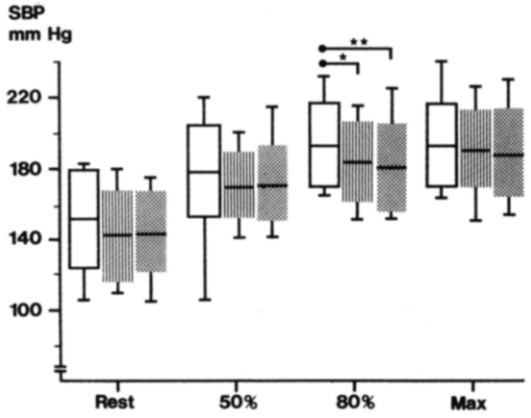


Figure 3. Systolic blood pressure (SBP) while sitting (rest) and during exercise. *p < 0.05; **p < 0.01. Other symbols and explanations as in Figure 2.

Rate-pressure product was significantly decreased (p < 0.001) at sitting rest and during all stages of exercise when comparing active treatment and placebo, but without any difference between diltiazem and verapamil.

Exercise capacity. The maximal work load attained during placebo treatment was 127 ± 39 W. Exercise tolerance increased to 136 ± 42 W (p < 0.01) during diltiazem and 137 ± 39 W (p < 0.01) during verapamil treatment. Maximal perceived exertion was 19.1 ± 0.3, 19.3 ± 0.7 and 19.2 ± 0.8 points on the Borg scale, respectively (p = NS).

Respiratory variables. Oxygen uptake (Fig. 4) during different treatments was similar at submaximal exercise levels. Maximal oxygen uptake during placebo treatment was 22.3 ± 4.5 ml/kg per min; the corresponding values for diltiazem and verapamil were 23.7 ± 4.9 (p < 0.05) and 22.9 ± 4.5 (p = NS), respectively. The difference between the two drugs was not significant (p = 0.074).

Minute ventilation was also similar at submaximal work loads during all treatment periods. The maximal ventilation was 69 ± 21 for placebo, 75 ± 26 (p = NS) for diltiazem and 74 ± 23 liters/min (p = NS) for verapamil.

Respiratory exchange ratio. The response pattern was the same as for other respiratory variables. Maximal values attained were 1.13 ± 0.08 with placebo, 1.15 ± 0.11 (p = NS) with diltiazem and 1.16 ± 0.11 (p = NS) with verapamil.

The anaerobic threshold could not be determined in one patient with chronic bronchitis and during one test in another patient because of air leakage from the mouthpiece. Values were compared among the 16 patients in whom complete data were obtained. The correlation between the two observers was r = 0.980.

During the placebo period, the criteria for the gas exchange anaerobic threshold were met at a work load of 76 ± 21 W (60 ± 17% of maximum), corresponding to an oxygen uptake of 16.2 ± 2.4 ml/kg per min. The corresponding values were 84 ± 27 W (p < 0.05, 62 ± 20% of maximum) and 16.9 ± 3.0 ml/kg per min for diltiazem and 85 ± 23 W (p < 0.01, 62 ± 17% of maximum) and 16.6 ± 3.0 ml/kg per min for verapamil.

Drug concentrations. The distribution of serum digoxin concentrations during the different treatments is shown in Table 1. Plasma diltiazem concentration was 453 ± 184 ng/ml (range 57 to 757); the corresponding value for plasma verapamil was 175 ± 107 ng/ml (range 36 to 495).

Side effects. The withdrawal of one patient was due to ankle edema during the second treatment period (diltiazem). All other suspected side effects are listed in Table 2.

Table 1. Serum Digoxin Concentrations (nmol/liter)

Digoxin	Placebo	Diltiazem	Verapamil
<0.6	8	6	4
0.6–1.0	6	8	8
>1.0	3	3	5

Data are derived from 17 of the 18 patients receiving digoxin; there was no significant difference between treatments.

Figure 4. Oxygen uptake (VO_2) during exercise. Symbols and explanations as in Figures 2 and 3.

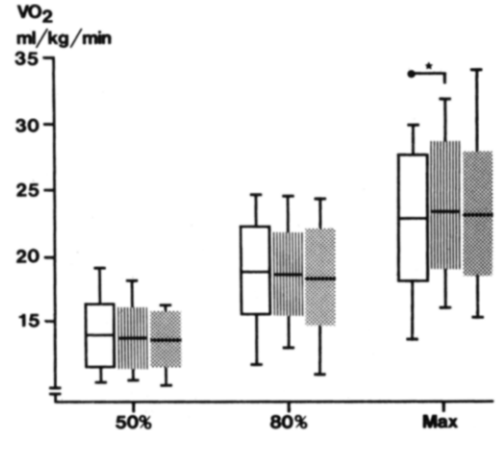


Table 2. Number of Side Effects in 18 Patients

	Placebo	Diltiazem	Verapamil
Ankle edema	4	8	8
Fatigue	4	6	8
Dizziness	4	4	3
Constipation	1	3	6
Flatulence/diarrhea	3	2	4
Headache	2	4	2
Other	7	9	10
Total	25	36	41

Discussion

Improvement in rate control with diltiazem and verapamil. The results of this study indicate that the ventricular rate control achieved with the calcium channel blockers diltiazem and verapamil improves exercise performance in chronic atrial fibrillation. The reduction in maximal ventricular rate after diltiazem (11%) and verapamil (12%) in the present study is somewhat less than the 17% to 22% reduction reported by others (4,7–9). This difference may partly be due to our comparatively low serum digoxin levels. It has been shown (4) that the addition of digoxin to calcium channel blocker therapy improves rate regulation during exercise. Verapamil interacts with digoxin (7), but the changes in serum digoxin in this study were insignificant and, thus, should not affect the comparisons among treatments. The influence of diltiazem and verapamil on ventricular rate was of the same magnitude both at rest and during exercise. Neither drug affected the normal pattern of heart rate changes over 24 h.

Active treatment increased the maximal exercise tolerance by 7% to 8%. It may be argued that the patients became accustomed to the testing procedure after the first test and that this contributed to the improvement in the subsequent tests. Still, the perceived exertion was unaltered at various work loads, including the maximal work load, and there was only a small insignificant change in the maximal respiratory exchange ratio. The delayed response in gas exchange anaerobic threshold is also consistent with a moderate but positive influence on exercise performance.

Mechanisms of improvement. The exact mechanism underlying the improvement is not clear. The individual response to treatment varies considerably, which is easily appreciated from the upper and lower ranges indicated in Figures 2 to 4. Improved diastolic filling through ventricular rate reduction would be expected to affect cardiac output and exercise performance, preferably at high heart rates close to maximal exertion. Maximal oxygen uptake was, however, significantly increased only with diltiazem. Conversely, the change in anaerobic threshold indicates an improved peripheral metabolic response to exercise for both drugs. The ventilatory anaerobic threshold is a reproducible index of the increase in blood lactate (16,17), and a delay in this point is seen after physical training both in normal subjects and in patients with chronic heart failure (18,19).

Previous exercise testing in patients with chronic atrial fibrillation on calcium channel blocker therapy has yielded divergent results (7–10). The lack of improvement in exercise capacity in two studies of diltiazem (8,9) may have been due to an excessive lowering of maximal heart rate to 133 to 142 beats/min. In the present investigation, heart rate was reduced from a high mean value of 179 to 159 beats/min, which is close to the normal age-predicted maximal heart rate (20). An impressive increase in exercise capacity was reported when verapamil decreased maximal heart rate from 165 to 136 beats/min (7). These results were not confirmed by a more recent study (10) or by our data. The relation between ventricular rate response and exercise capacity seems to be complex. The variability in the reported effects of calcium channel blockers may also depend on the inhomogeneity of the patients in various studies.

It has been suggested (21) that a high maximal heart rate may compensate for the loss of atrial function in exercising patients with chronic atrial fibrillation. Our findings do not support that hypothesis. There were no negative effects on exercise capacity or gas exchange variables in our patients despite a substantial reduction in ventricular rate. Studies (22) in pacemaker-treated patients have also demonstrated that atrial function is of minor importance at high heart rates.

It may be assumed that after ventricular rate reduction, an adequate blood supply is maintained in exercising muscles through an increase in left ventricular diastolic filling, which results in an augmentation of stroke volume. Thus, possible negative inotropic effects of the calcium channel blockers seem to be counteracted by a positive Frank-Starling effect. A negative drug effect causes an earlier-appearing anaerobic threshold and a lower maximal oxygen uptake. In chronic atrial fibrillation, such a response is produced by the beta-blocker celiprolol (23). No consistent differences were found between diltiazem and verapamil in these respects; hence, it seems that any difference in negative inotropy of the two drugs is negligible when they are given in doses with comparable negative dromotropic responses. The conformity of the effects on systolic blood pressure also suggest similar vasodilating properties. These results are in contrast to findings in experimental studies (24,25), in which verapamil caused more potent negative inotropic and dromotropic effects when the drugs were administered in equihypotensive doses.

Clinical implications. Chronic atrial fibrillation is often associated with and may precede congestive heart failure (26,27). This association is found even in the absence of other overt cardiovascular disease. Myocardial energy depletion, which is promoted by a high myocardial work load, has been suggested as an important factor in the development of heart failure (28). Calcium channel blockers may interfere in this process in patients with chronic atrial fibrillation, because the rate-pressure product is reduced substantially by treatment with diltiazem and verapamil. As a consequence, myocardial oxygen consumption and energy demand are reduced. Importantly, this is achieved without compromising cardiocirculatory function.

Side effects. As indicated in Table 2, typical side effects of calcium channel blockers (for example, edema and constipation) were more frequent during active treatment. These side effects are known to be dose dependent (4,10). Paradoxically, fatigue was reported by some patients despite increased exercise capacity. This may relate to excessive

JACC Vol. 16, No. 1
July 1990:86–90

ventricular rate reduction at rest. Taken together, these observations emphasize the need for individual dose titration.

Conclusions. Diltiazem and verapamil are both effective agents in the treatment of patients with chronic atrial fibrillation. The negative dromotropic effect and the influence on exercise performance do not seem to differ when the two drugs are administered in the present dosage.

We acknowledge Anna-Lena E:son-Loft for help in preparing the manuscript and Östen Karlsson for technical assistance.

References

1. Åberg H, Ström G, Werner I. Heart during exercise in patients with atrial fibrillation. Acta Med Scand 1972;191:315–20.
2. Corday E, Irvine DW. Disturbances of Heart Rate, Rhythm and Conduction. Philadelphia: WB Saunders, 1961:207.
3. Beasley R, Smith DA, McHaffie DJ. Exercise heart rates at different serum digoxin concentrations in patients with atrial fibrillation. Br Med J 1985;290:9–11.
4. Roth A, Harrison E, Mitani G, Cohen J, Rahimtoola SH, Elkayam U. Efficacy and safety of medium- and high-dose diltiazem alone and in combination with digoxin for control of heart rate at rest and during exercise in patients with chronic atrial fibrillation. Circulation 1986;73: 316–24.
5. Klein HO, Pauzner H, DiSegni E, David D, Kaplinsky E. The beneficial effects of verapamil in chronic atrial fibrillation. Arch Intern Med 1979; 139:747–9.
6. Stone PH, Antman EM, Muller JE, Braunwald E. Calcium channel blocking agents in the treatment of cardiovascular disorders. Ann Intern Med 1980;93:886–904.
7. Lang R, Klein HO, DiSegni E, et al. Verapamil improves exercise capacity in chronic atrial fibrillation: double-blind crossover study. Am Heart J 1983;105:820–5.
8. Steinberg JS, Katz RJ, Bren GB, Buff LA, Varghese PJ. Efficacy of oral diltiazem to control ventricular response in chronic atrial fibrillation at rest and during exercise. J Am Coll Cardiol 1987;9:405–11.
9. Atwood JE, Myers JN, Sullivan MJ, Forbes SM, Pewen WF, Froelicher VF. Diltiazem and exercise performance in patients with chronic atrial fibrillation. Chest 1988;92:20–5.
10. Lewis R, Lakhani M, Moreland TA, McDevitt DG. A comparison of verapamil and digoxin in the treatment of atrial fibrillation. Eur Heart J 1987;8:148–53.
11. Smith TW, Butler VP, Haber E. Determination of therapeutic and toxic serum digoxin concentrations by radioimmunoassay. N Engl J Med 1969;281:1212–6.
12. Wiens RE, Runser DJ, Lacz JP, Dimmitt DC. Quantitation of diltiazem and desacetyl diltiazem in dog plasma by HPLC. J Pharm Sci 1984;73: 688–9.
13. Anderson P, Bondesson U, Sylvén C. Clinical pharmacokinetics of verapamil in patients with atrial fibrillation. Eur J Clin Pharmacol 1982; 23:49–57.
14. Borg GAV. Physical Performance and Perceived Exertion (thesis). Lund, Sweden: Berlingska Boktryckeriet, 1962:39–41.
15. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986;60:2020–7.
16. Simonton CA, Higginbotham MB, Cobb FR. The ventilatory threshold: quantitative analysis of reproducibility and relation to arterial lactate concentration in normal subjects and in patients with chronic congestive heart failure. Am J Cardiol 1988;62:100–7.
17. Matsumura N, Nishijima H, Kojima S, Hashimoto F, Minami M, Yasuda H. Determination of anaerobic threshold for assessment of functional state in patients with chronic heart failure. Circulation 1983; 68:360–7.
18. Davis JA, Frank MH, Whipp BJ, Wasserman K. Anaerobic threshold alterations caused by endurance training in middle-aged men. J Appl Physiol 1979;46:1039–46.
19. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with chronic heart failure delays ventilatory anaerobic threshold and improves submaximal exercise performance. Circulation 1989;79:324–9.
20. Åstrand I. Aerobic work capacity in men and women with special reference to age. Acta Physiol Scand 1960;49(suppl 169):1–92.
21. Atwood JE, Myers J, Sullivan M, et al. Maximal exercise testing and gas exchange in patients with chronic atrial fibrillation. J Am Coll Cardiol 1988;11:508–13.
22. Kristensson B-E, Arnman K, Rydén L. The haemodynamic importance of atrioventricular synchrony and rate increase at rest and during exercise. Eur Heart J 1985;6:773–8.
23. Atwood JE, Sullivan M, Forbes S, et al. Effect of beta-adrenergic blockade on exercise performance in patients with chronic atrial fibrillation. J Am Coll Cardiol 1987;10:314–20.
24. Urquhart J, Patterson RE, Bacharach SL, et al. Comparative effects of verapamil, diltiazem and nifedipine on hemodynamics and left ventricular function during acute myocardial ischemia in dogs. Circulation 1984;69: 382–90.
25. Nakaya H, Schwartz A, Millard RW. Reflex chronotropic and inotropic effects of calcium-channel blocking agents in conscious dogs. Circ Res 1983;53:302–11.
26. Godtfredsen J. Atrial Fibrillation: Etiology, Course and Prognosis—a Follow-Up Study of 1212 Cases (thesis). Copenhagen: University of Copenhagen, 1975.
27. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham Study. N Engl J Med 1982;306:1018–22.
28. Katz AM. Cellular mechanisms in congestive heart failure. Am J Cardiol 1988;62:3A–8A.